Troponin T elevation in amyotrophic lateral sclerosis without cardiac damage

Hof, D ; Jung, H H ; Bloch, K E

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Running title: Troponin T in ALS without cardiac damage

Danielle Hof, PhD [1], Hans H. Jung, MD [2], Konrad E. Bloch, MD [3]

[1] University Hospital Zurich, Institute for Clinical Chemistry, Zurich, Switzerland

[2] University Hospital Zurich, Department of Neurology and Neuromuscular Center, Zurich, Switzerland

[3] University Hospital Zurich, Pulmonary Division and Neuromuscular Center, Zurich, Switzerland

Corresponding author:

Konrad E. Bloch

University Hospital Zurich, Pulmonary Division and Neuromuscular Center

Raemistrasse 100

CH-8091 Zurich, Switzerland

E-mail: konrad.bloch@usz.ch

Telephone: +41-(0)44-2553828

Fax: +41-(0)44-2554451

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A 65-year old man presented in May 2010 with progressive weakness of arms over the course of several weeks, dysarthria and signs of upper and lower motoneuron dysfunction with atrophic tetraparesis, fasciculations, spasticity, and hyperreflexia. After exclusion of other differential diagnoses by extensive evaluations, clinically definite ALS was confirmed (1). ALS functional rating was 29 of 48 points. Riluzole treatment was started. In September 2011, the patient was admitted with acute chest discomfort and nocturnal dyspnoea. Acute pulmonary embolism, pneumothorax and other abnormalities were ruled out by contrast-enhanced computed tomography. An electrocardiogram was normal. The patient was discharged after 12 hours observation and resolution of symptoms. Two weeks later, he presented with nocturnal dyspnoea and epigastric discomfort. Cardiac markers were slightly elevated (Table), raising the possibility of acute coronary syndrome (ACS). N-terminal prohormone of brain natriuretic peptide, plasma creatinine, arterial blood gases and electrocardiogram were normal. Single-photon emission computed tomography (SPECT) with adenosine stimulation revealed a normal cardiac contraction and no evidence of ischemia or scarring. Over the course of 2 days, no changes in the cardiac troponin T (cTnT) levels were noted. Spirometry was normal. A sleep study suggested borderline sleep-related alveolar hypoventilation and mild central sleep apnoea. Nocturnal positive airway pressure ventilation was initiated and pantoprazole (40 mg/d) started for presumed gastritis. He continued the nocturnal ventilation at home. Laboratory tests were repeated after 2 weeks (Table). It was concluded that the most likely causes of the dyspnea and epigastric discomfort were sleep-related breathing disturbances and gastritis. The initial suspicion of myocardial injury was rejected.

According to international guidelines, diagnosis of ACS relies on electrocardiogram and repeated measurements of cTn (2), but the case described here underlines the importance of considering differential diagnoses other than ACS as causes of elevated markers of myocardial necrosis. A moderate creatine kinase (CK) elevation (up to 1000 U/l) is common

in ALS patients and may reflect neurogenic muscle atrophy (3). Raised levels of CK-MB and myoglobin may origin from various non-cardiac sources. In contrast, the specificity and sensitivity of cTnT for cardiac muscle injury is much higher, and its sensitivity increased in particular with novel high-sensitivity assays (4). A few rare circumstances with elevated cTn of non-cardiac origin have been described (5), but could be excluded in the described ALS patient. Interfering antibodies that could lead to falsely high cTn levels (6) were unlikely, since incubation of the patient's plasma with a heterophilic blocking reagent left the cTn concentration unchanged (Table). Diluting his sample in cTnT-free plasma demonstrated an ideal dilution curve (not shown), corroborating the absence of interfering antibodies. Recently, an ALS patient with chronically elevated levels of cTnT and cardiac troponin I (cTnI) was described (7). He had very advanced disease with chronic hypoventilation, and the authors ascribed the elevation of cTnT to myocardial hypoxia. Hypoxemia is an unlikely explanation of the isolated cTnT elevation without associated cTnI elevation in the current patient, since his daytime blood gases were normal and nocturnal oxygen saturation rarely dropped below 90%. Cases of cTnT without cTnI elevation have been reported (8), although the origin remained speculative. A potential mechanism is the expression of cTn isoforms in non-cardiac cells, as observed in muscle biopsies from patients with skeletal muscle myopathies (9). Although the ALS patient presented here did not suffer from a myopathy, similar atypical cTn expression in other, unexpected cell types may have occurred. However, the cause of his laboratory anomalies remained unclear.

We report the first case of an ALS patient in whom respiratory failure could not explain the cTnT elevation and several other causes of cTnT elevations had been specifically ruled out. In ALS patients presenting with symptoms of ACS, cTn should be measured at defined time intervals to capture the rise and/or fall of cTn which is highly suggestive of ACS (10). Non-dynamic elevations of cTn may derive from causes other than myocardial damage. Most importantly, laboratory data should be interpreted in view of patient history, clinical

presentation and electrocardiogram before further invasive and costly examinations are performed.

5

Table. Laboratory and clinical examinations

Plasma measurements of cardiac markers				
	Ref	**Sample 1, on admission**	**Sample 2, 2 weeks later**	
			Untreated	**treated with HBT**
NT-proBNP (ng/l)	< 376	81	n.d.	43
Myoglobin (µg/l)	28 - 72	131	118	113
CK (U/l)	< 190	445	338	338
CK-MB (U/l)	< 24	33	26	27
CK-MB/CK ratio (%)	<6.0	7.4	7.7	8.0
cTnT (µg/l)	< 0.014	0.103	0.166	0.166
cTnI (µg/l)	< 0.040	n.d.	< 0.040	< 0.040
Arterial blood gas analysis spontaneously breathing room air on admission				
pH	7.35-7.45	7.473		
$PaCO_2$ (kPa)	4.5-6.0	3.98		
PaO_2 (kPa)	>10.0	13.1		
Bicarbonate (mmol/l)	22-26	23.9		
Pulmonary function on admission				
FVC (L, % pred)	4.31	4.27 (99%)		
FEV1 (L, % pred)	3.34	3.05 (91%)		
Sniff nasal pressure, mbar	85	64		
Sleep study during first night after admission				
Mean nocturnal oxygen saturation (%)	>90	94		
Oxygen saturation <90% (% TIB)	0	1		
Apnea/hypopnea index (events/h)	<5	15/h		
Nocturnal rise in $PtcCO_2$ (mmHg)	<10	9		

NT-proBNP = N-terminal prohormone of brain natriuretic peptide; CK = creatine kinase, CK-MB = creatine kinase MB isoform; cTnT = cardiac troponin T by high-sensitivity immuno-assay, Roche Diagnostics, Switzerland (4^{th}-generation assay: 99^{th} percentile of 0.014 µg/l, coefficient of variation ≤ 10% at this concentration); cTnI = cardiac troponin I by automated immunoassay, AccuTnI, Beckman Coulter (99^{th} percentile of 0.040 µg/l, coefficient of variation of 14% at this concentration); HBT = heterophilic blocking reagent tube, n.d. = not determined; FVC, FEV1 = forced vital capacity and expiratory volume in 1 s; $PtcCO_2$=transcutaneous PCO_2; % TIB= percent of time in bed

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